REMARKS

Amendments to the Claims

Claims 5, 10 and 18 are cancelled. Claims 6, 7, 11-14 and 16-17 are amended. Claim 33 is added.

Claim 6 has been amended to recite "The method of Claim 1, wherein the cells are administered to the disc using a carrier, wherein the carrier is selected from the group consisting of beads, microspheres, nanospheres, hydrogels, gels, polymers, ceramics, collagen and platelet gels." Support is found in the specification, for example, at page 7, lines 10-13.

Claim 7 has been amended to recite "The method of Claim 1, wherein an additional therapeutic agent is administered into the intervertebral disc, and wherein said additional therapeutic agent is TGF-β." Claims 12-14 have been amended to recite that the additional therapeutic agent is TGF-β. Support is found in the specification, for example, at page 10, lines 5-27.

Claim 11 has been amended to recite "The method of Claim 7, wherein the TGF-β and the cells are administered into the intervertebral disc using a carrier, wherein the carrier is selected from the group consisting of beads, microspheres, nanospheres, hydrogels, gels, polymers, ceramics, collagen and platelet gels." Support is found in the specification, for example, at page 7, lines 10-13 and page 10, lines 5-27.

Claims 16 and 17 have been amended to alter their dependency.

New Claim 33 recites "A method of treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc immediately following harvesting of the autologous uncultured mesenchymal stem cells." Support is found in the specification, for example, at page 4, line 22 to page 5, line 5.

No new matter has been added. Therefore, entry of the amendments into the application is respectfully requested.

Office Action

Applicants note that their representative, Deirdre Sanders, confirmed with the Examiner that the pending Office Action is a non-final Office Action.

Priority

The Examiner states that USSN 10/456,948 (the '948 application) fails to provide adequate support or enablement for claims directed to treatment with mesenchymal stem cells. Applicants respectfully disagree and maintain their arguments regarding priority as stated in the Amendment filed December 7, 2006. The Examiner finds that the '948 application does contain prophetic teachings of treatment with mesenchymal stem cells. However, it is not clear why the Examiner believes that these teachings do not meet the enablement requirements of 35 U.S.C. § 112, first paragraph. Prophetic examples can be used to provide enabling support to claims. Reports of actual data are not required. All that is required is that the person of skill in the art could make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). On page 21, line 28 to page 22, line 9, the '948 application discloses administering autologous mesenchymal stem cells in accordance with the claimed invention. As indicated in the previous Amendment and as discussed further below, the claims were enabled by the disclosure in the '948 application, and are entitled to its filing date.

Rejection of Claims 1-7, 10-18, 20-24 and 31-32 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claims 1-7, 10-18, 20-24 and 31-32 under 35 U.S.C. § 112, first paragraph as lacking enablement, for reasons of record.

Applicants respectfully disagree. The claims are enabled because the person of skill in the art could make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

Autologous Uncultured Mesenchymal Stem Cells

The Examiner states that "Applicant argues first that amendment from 'autologous cells' to 'mesenchymal cells' in claim 1 obviates the rejection." Applicants direct the Examiner's attention to the fact that in the Amendment filed on December 7, 2006, Applicants amended Claim 1 to recite "*autologous uncultured* mesenchymal stem cells," not "mesenchymal cells."

The Examiner also indicates that this amendment and the accompanying argument is not persuasive because "many of the other limitations outside the scope of enablement are not included in base claim 1 or any other claims." However, the fact that limitations outside the scope of enablement are not included in the claim does not appear to be a ground to find lack of enablement. Applicants respectfully request clarification of this position. Further, the only claim elements that are discussed in the enablement rejection regard growth factors and carriers, yet many of the rejected claims do not include these elements. Moreover, on pages 2-3 of the Office Action the Examiner states that "the earliest time at which the invention can be considered enabled by the prior art is at application 10/714,559, filed 11/13/03." Thus, the Examiner appears to agree that the claimed invention is at least enabled as of November 13, 2003, the filing date of the parent. Thus, it is unclear as to why enablement rejections have been asserted by the Examiner with regard to Claim 1 and claims depending from Claim 1.

Applicants' specification provides ample teachings to enable the claimed method of treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc. See the specification, for example, at page 4, line 22 to page 5, line 25 and page 6, line 8 to page 9, line 9 and page 11, line 11, page to page 13, line 14. One of skill in the art can practice the claimed invention without undue experimentation and the claims are enabled.

Growth Factor

The Examiner states that Claims 7 and 18 are not enabled because "some growth factors actually inhibit proliferation of chondrocytes, which would destroy the instant invention," and, therefore, the method would not work with a generic growth factor. The Examiner cites Raucci, A. *et al.*, "Activation of the ERK1/2 and p38 Mitogen-Activated Protein Kinase Pathways Mediates Fibroblast Growth Factor-Induced Growth Arrest of Chondrocytes," *J. Biol. Chem.*, *279*(3):1747-1756 (2004) ("Raucci") and states that this reference teaches that both NGF and bFGF inhibit proliferation of chondrocytes both *in vitro* and *in vivo*.

Applicants respectfully disagree. First, Raucci does not clearly teach that NGF inhibits proliferation of chondrocytes *in vivo*. Raucci states that, although NGF treatment of transfected rat chondrosarcoma cells (RCS) caused growth inhibition, EGF treatment did not. Moreover,

Raucci teaches that the inhibition of proliferation of chondrocytes by FGF is a "complex event" that requires the intervention of several proteins. Therefore, it is not clear that Raucci's teachings are applicable for determining the enablement of Applicants' claimed invention. Accordingly, Raucci does not establish that administration of growth factors in the context of Applicants' claimed methods (Claims 7 and 18) is not enabled.

Nonetheless, while Applicants disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to expedite prosecution, Applicants have canceled Claim 18. Claim 7, as amended, recites TGF-β. NGF is a member of the nerve growth factor family and bFGF is a member of the fibroblast growth factor family. In contrast, TGF-β, is a member of the transforming growth factor superfamily. Further, Sakai, cited by the Examiner, teaches culturing in the presence of TGF-β1, which is a member of the TGF-β superfamily, and does not teach that TGF-β1 inhibited proliferation of chondrocytes.

Applicants' specification provides a description of the administration of TGF-β. See the specification, for example, at page 10, lines 13-29. Further, administration of such a growth factor is well known in the art. It would not be beyond the ken of one of skill in the art to administer TGF-β1 in the invention claimed in Claim 7.

Carrier

The Examiner states that "Applicant lastly argues on page 9 of Remarks that a carrier medium that does not cause retention of mesenchymal cells at the site of placement is useful."

Applicants respectfully disagree with this characterization of Applicants' position. Applicants' position is that a carrier that does not cause *long term* retention of mesenchymal stem cells is useful in the claimed invention. On page 9 of the Amendment referenced by the Examiner (filed on December 7, 2006), Applicants were responding to the Examiner's statement in the previous Office Action dated September 7, 2006, that post-filing date art suggests that the carrier hyaluronan is not appropriate for use as a hydrogel for long-term retention of mesenchymal cells at the locus of action of the degenerative disc disease. According to the Examiner, although it possesses several desirable properties, it does not result in long-term retention of such cells, and, thus, predictability of the appropriate carrier is low. Applicants responded by stating that "contrary to the Examiner's position, it is not necessary, and, in fact, it

may be undesirable, to use carriers that retain cells long term when treating degenerative disc disease." (emphasis added) This is because there is limited space in the degenerative disc space and because the mesenchymal stem cells, once delivered to the degenerative disc space, begin to act on their own without the need for a carrier. Once the stem cells start to become nucleus pulposus and start to form the matrix, carriers are no longer needed. Thus, a carrier that retains mesenchymal cells at the site of placement is useful, but a long-term carrier is not necessary.

In addition, the Examiner cites Crevensten *et al.*, "Intervertebral Disc Cell Therapy for Regeneration" Mesenchymal Stem Cell Implantation in Rat Intervertebral Discs," *Annals of Biomedical Engineering, 32*:43-434 (2004) (hereinafter "Crevensten") at page 433, right column and states that hyaluronan was found to be toxic to the cells at 15%.

Applicants note that, on page 433 of Crevensten, the authors consider several potential explanations for the observed decrease in the population of injected cells at 7 and 14 days. The authors posit that perhaps the high initial concentration of hyaluronan "may have" been cytotoxic since nuclear tissue obtained from 7 and 14 day discs contained fewer native cells. However, they also state that other explanations are possible, such as the fact that the fluorescent membrane may have faded and could no longer be detected or that the decrease in cells may be due to expulsion of nuclear material. They conclude that the decrease in cell number "may" be related to cell death or expulsion of some injected cells before the injection tract could heal. (*Id.* at page 434). However, in the next sentence they note that "nonetheless, the remaining cells did proliferate over the next 3 weeks". Thus, Crevensten was merely hypothesizing about the reasons for the reduction of the number of injected cells post injection. Crevensten does not conclusively teach that the hyaluronan was, in fact, toxic to the cells, or that it would be toxic in Applicants' methods.

In fact, hyaluronan (also known as hyaluronic acid) is a natural component of the extracellular matrix. It is known to be routinely used safely and effectively in humans. Hyaluronan acid-based materials have replaced animal or human-derived collagen as standard injection materials. For example, ORTHOVISC® is a sterile mixture made from purified hyaluronan dissolved in saline. It is marketed for injection into the knee to provide relief from knee pain caused by osteoarthritis (see Exhibit A, printed pages from the website www.orthovisc.com). Administration of carriers including hyaluronan are well known in the art

and are taught in Applicants' specification. Therefore, Applicants' claims directed to use of carriers that include hyaluronan in their scope are enabled.

Reconsideration and withdrawal of the rejections is respectfully requested.

Rejection of Claims 1-3, 5-6, 10-16, 20-24 and 31 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-3, 5-6, 10-16, 20-24 and 31 under 35 U.S.C. § 103(a) as being unpatentable over Sakai *et al.*, "Transplantation of Mesenchymal Stem Cells Embedded in Atelocollagen® Gel to the Intervertebral Disc: A Potential Therapeutic Model for Disc Degeneration," *Biomaterials, 24*: 3531-3541 (September 2003) ("Sakai").

With regard to publication date, as Applicants have indicated above, Applicants believe that the application is entitled to a priority date which is before the publication date of Sakai. Therefore, Sakai should not be eligible as prior art. The Examiner also indicates that the earliest publication of Sakai is an abstract from the Annual Meeting of the International Society for the Study of the Lumbar Spine, dated May 2003 ("Abstract"). The Examiner does not appear to be relying on this abstract in a new obviousness rejection. Regardless of its publication date, the Abstract does not provide the teachings to render Applicants' invention obvious.

Sakai does not teach or suggest Applicants' claimed invention. Applicants are the first to disclose treatment of degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc. Sakai discloses use of cultured mesenchymal stem cells for the treatment of intervertebral disc degeneration, using a rabbit model. One of ordinary skill in the art would not be motivated to practice Applicants' claimed invention of using uncultured mesenchymal stem cells with a reasonable expectation of success.

The art teaches that culturing was standard practice at the time of the invention

The Examiner further states that: "Sakai practices a more difficult method in culturing mesenchymal cells in order to label them, but also in order to expand them, because Sakai *et al.* demonstrate the viability of cells after two weeks of culturing." (page 5) Applicants agree that Sakai cultured the cells in order to expand them. The published Abstract also indicates that the MSCs were isolated from marrow and cultured for 2 weeks.

Applicants maintain their arguments from the Amendment filed December 7, 2006 and further state that, at the time of the invention, culturing was generally used not only to mark cells, but also to expand and differentiate cells. It was standard practice in the art to culture clinically useful cells. The following discussion of references published at the time of the invention all teach culturing clinically useful cells outside of the context of marking, and demonstrate that one of ordinary skill in the art at the time of the invention would be motivated to culture cells prior to administration. These references were also cited in the IDS filed on November 14, 2003.

The following summary of the references is taken from the specification at pages 2-4 and presented below:

> U.S. Patent No. 6,352,557 ("Ferree") teaches adding therapeutic substances such as nucleus pulposus cells to morselized extra-cellular matrix obtained from donors, and injecting that combination into an intervertebral disc. However, the cells first need to be cultured and then added to the donor matrix prior to implantation into the diseased disc. This process requires a delay in the patient's treatment in addition to subjecting the patient to two separate procedures. The first procedure is to harvest the cells, which then require culturing. Following the culturing the cells are implanted into the patient.
>
> U.S. Patent No. 6,340,369 ("Ferree II") teaches harvesting live intervertebral disc cells from a patient, culturing the cells and transplanting them into the affected disc.
>
> (emphasis added)
>
> Ferree II further teaches that the cells can be combined with Type II collagen-glycosaminoglycan matrix or Type I collagen-glycosaminoglycan matrix depending on whether the cells are harvested from the nucleus pulposus (NP) or annulus fibrosus (AF). Also Ferree II suggests adding one or more therapeutic substances to cells prior to transplantation. As an alternate source for cells, Ferree proposes using precursor cells of NP or AF cells, chondrocytes or other living cells that function like or could differentiate into NP or AF cells. Throughout, Ferree teaches that the harvested cells are cultured prior to transplantation.
>
> (emphasis added)

Alini, M., *et al.*, "A Biological Approach to Treating Disc Degeneration: Not for Today, but Maybe for Tomorrow," *Eur. Spine J., 11* (Suppl. 2): S215-S220 (2002) suggests that injection of a biomatrix embedded with cells will have the potential to restore functionality to the disc. Alini's experiments are directed to isolating cells from the nucleus pulposus and culturing them. Alini also suggests other sources of cells including disc cells from allogenic donors and autologous stem cells. His teachings suggest that stem cells would be an ideal source but that there are no known methods for culturing the stem cells such that they would differentiate into nucleus pulposus cells prior to implantation. In essence, Alini requires that cells be cultured prior to implantation.

(emphasis added)

Richardson, S., *et al.*, "Human Bone Marrow Mesenchymal Stromal Cells as a Source of Chondrocytes for Treatment of Intervertebral Disc Degeneration," 27, Abstracts of the 30th Annual Meeting of the International Society for the Study of the Lumbar Spine, Vancouver, Canada (May 2003) reports conducting an experiment to determine whether mesenchymal stem cells (MSCs) could be directed to present disc chondrocyte phenotypes. Russell found that adult human MSCs were induced to differentiate along a chondrocytic phenotype when mediated by culture conditions and also by addition of TGF-β1.

(emphasis added)

Sobajima, S., *et al.*, "Stem Cell Therapy for Degenerative Disc Disease: An In-Vitro Feasibility Study," 43, Abstracts of the 30th Annual Meeting of the International Society for the Study of the Lumbar Spine, Vancouver, Canada (May 2003) studied the feasibility of stem cell therapy for DDD. Human NP cells were isolated from patients undergoing disc surgery and were co-cultured with either MSCs from patients undergoing hip surgery or muscle derived stem cells from mice. The data demonstrated a synergistic effect between stem cells and nucleus pulposus cells, resulting in upregulated proteoglycan synthesis in vivo.

(emphasis added)

> Ganey, T. M. and Meisel, H. J., "A Potential Role for Cell-Based Therapeutics in the Treatment of Intervertebral Disc Herniation," Eur. Spine J., 11 (Suppl. 2): S206-S214 (2002), reported on surgeries conducted in Germany where cells were harvested from portions of a patient's disc after discectomy. The cells were then cultured and returned for transplantation into the patient at a later date.
>
> (emphasis added)

These references all require culturing of cells prior to implantation. These references demonstrate that one of ordinary skill in the art at the time of the invention would have been motivated to culture cells prior to implantation, in order to expand and differentiate cells.

Objective evidence of nonobviousness

Further, objective evidence of nonobviousness must be considered, as stated in the MPEP at § 2141 (August 2006 revision):

> Objective evidence or secondary considerations such as unexpected results, commercial success, long felt need, failure of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the examiner must evaluate the evidence.

The claimed invention has satisfied a long-felt need in the relevant field. The contemporaneous references discussed above require culturing of cells, which, in turn, necessitates a delay in treating the patient's degenerating disc. The fact that others in the field had tried for years to achieve a result, yet had failed, is evidence that the invention would not have been obvious to those skilled in the art when it was invented. Applicants' claimed method of administering uncultured mesenchymal stem cells is advantageous because the process permits the patient to undergo the procedure of removal of cells from the bone marrow while the patient is already under general anesthesia to undergo the surgery required to administer the cells to the degenerative disc. Nonetheless, Applicants' methods had not been performed prior to Applicants' application.

Impermissible hindsight

The Examiner states that Applicants' arguments that the method of Sakai cannot be used as a therapeutic are not persuasive because Sakai demonstrates the effectiveness of the treatment. The Examiner's conclusion that Sakai's method is therapeutically useful is based on impermissible hindsight using Applicants' specification. Sakai's method would result in magnifying contamination of the cell population.

Further, culturing stem cells involves expanding the cell population by adding solutions, such as Dulbecco's modified eagle media (DMEM). DMEM contains phenol which is a hazardous chemical to the human body. Sakai does not disclose how to overcome the DMEM toxicity. Moreover, Sakai's culturing of stem cells would not be desirable for treatment of degenerative disc disease because culturing results in a large stem cell population, which is not desirable to have a large stem cell population because one would not want to overburden the bodily system with nutritional requirements for feeding large numbers of such cells. In addition, the degenerative disc can only hold a limited number of cells.

Sakai's teachings merely demonstrate proof of the concept that autologous cultured mesenchymal stem cells delivered to a degenerating disc resulted in preservation of disc structure and differentiation of cells, providing "new hopes" for treatment of degenerative disc disease in humans. The Sakai Abstract merely concludes that "our study has implicated the potential of MSCs to differentiate into invertebral cells, which provides new information in MSC research." The Abstract does not establish that administration of uncultured autologous MSCs would be useful in Applicants' claimed invention. Sakai does not teach a therapeutic method for delivering uncultured mesenchymal stem cells.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-6, 10-16, 20-24 and 31 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-6, 10-16, 20-24 and 31 under 35 U.S.C. § 103(a) as being unpatentable over Sakai in view of Tanny, G.B. *et al.*, "Improved Filtration Technique for Concentrating and Harvesting Bacteria," *Appl. Environ. Microbiol., 40*(2):269-273 (1980).

As indicated above, Sakai does not teach a therapeutic method for delivering uncultured mesenchymal stem cells. Tanney teaches concentrating cells by filtration and harvesting bacterial cultures. As discussed in Tanney, the bacterial cells were cultured. The Examiner's combination of these two references, which teach culturing of cells, reinforces Applicants' argument that culturing was standard practice at the time of the invention. None of the references alone or teach in combination teach or suggest treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc. One of ordinary skill in the art would not be motivated to combine the teachings of Sakai with Tanney, based on these references or the knowledge of one of ordinary skill in the art, with any reasonable expectation of success in treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc. Therefore, the invention is not obvious.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-3, 5-7, 10-17, 18, 20-24 and 31-32 under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-3, 5-7, 10-17, 18, 20-24 and 31-32 under 35 U.S.C. § 103(a) as being unpatentable over Sakai in view of Russell *et al.* "Human Bone Marrow Mesenchymal Stromal Cells as a Source of Chondrocytes for Treatment of Intervertebral Disc Degeneration," 27, Abstracts of the 30th Annual Meeting of the International Society for the Study of the Lumbar Spine, Vancouver, Canada (May 2003).

As indicated above, Sakai does not teach a therapeutic method for delivering uncultured mesenchymal stem cells. Russell teaches the use of human bone marrow mesenchymal stromal cells as a source of chondrocytes for the treatment of intervertebral disc degeneration. In addition, Russell teaches that the mesenchymal stem cells were cultured in the presence of TGF-β1. The Examiner's combination of these two references, which teach culturing of cells, reinforces Applicants' argument that culturing was standard practice at the time of the invention. None of the references alone or teach in combination teach or suggest treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc. One of ordinary skill

in the art would not be motivated to combine the teachings of Sakai with Russell, based on these references or the knowledge of one of ordinary skill in the art, with any reasonable expectation of success in treating degenerative disc disease in an intervertebral disc having a nucleus pulposus, comprising administering autologous uncultured mesenchymal stem cells into a degenerated intervertebral disc. Therefore, the invention is not obvious.

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Reconsideration and withdrawal of the rejection are respectfully requested.

Information Disclosure Statement

Applicants respectfully request acknowledgement and consideration of the Supplemental Information Disclosure Statement filed on February 26, 2007 and April 13, 2007.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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Date: June 12, 2007

What Is ORTHOVISC®?

ORTHOVISC® is a viscous (thick) sterile mixture made from highly purified hyaluronan dissolved in saline. Hyaluronan is a natural chemical found in the joint fluid of your body. The body's own hyaluronan acts like a lubricant and a shock absorber in the joint. It is needed for the joint to work properly.

ORTHOVISC® is ultra-pure hyaluronan, which contains no buffers or preservatives. ORTHOVISC® contains the highest concentration of hyaluronan available per injection. [1]

What is ORTHOVISC® used for?

ORTHOVISC® is used to relieve knee pain due to osteoarthritis (OA). It is used for patients who do not get adequate pain relief from simple pain relievers like acetaminophen or from exercise and physical therapy.

How can you get ORTHOVISC®?

ORTHOVISC® is given by a trained healthcare professional, usually an orthopedic surgeon or rheumatologist. Your family doctor can refer you to one of these specialists. To find out more, talk to your doctor or physical therapist.

Learn how ORTHOVISC® works.

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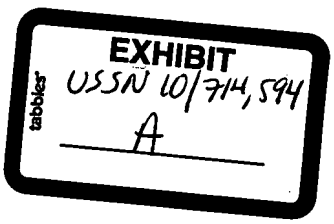
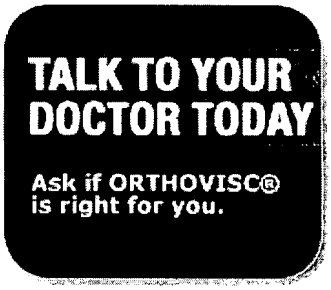
[1]Competitive Package Insert comparison, October 2005.



How does ORTHOVISC® Work?

In healthy knees, the space between the bones is filled with a thick and slippery liquid (joint fluid). Joint fluid acts like a shock absorber to give your knee cushioning while walking, working, or playing sports.



When you have osteoarthritis, your body's joint fluid becomes less healthy and the cartilage begins to break down, leading to irritation and discomfort in the knee.

ORTHOVISC® is injected directly into the knee, where it may help restore the cushioning properties of your joint fluid. This can provide up to six months of relief from knee pain. [1]

How is ORTHOVISC® used?

ORTHOVISC® is given as an injection. Your doctor will inject ORTHOVISC® into your knee once a week, for a total of three or four injections. This can usually be done right in the doctor's office.

Are there any special instructions for the treatment?

Before treatment, tell your healthcare provider if you are allergic to products from birds, such as eggs, poultry, or feathers.

After your injections, it is recommended that for 48 hours you avoid activities such as jogging, tennis, heavy lifting, or standing on your feet for a long time (more than one hour).

Find out if ORTHOVISC® is right for you.

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[1]Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT, et al. Efficacy and Safety of Intraarticular Sodium Hyaluronate in Knee Osteoarthritis. *Clinical Orthopaedics and Related Research.* 2001;385:130-143.